



Chemical Space of Auxins, their Multi-Phenomenology and Multiple Protein Interaction

N. Ferro, P. Bultinck, Th. Bredow, Th. Reinard

published in

From Computational Biophysics to Systems Biology (CBSB07),
Proceedings of the NIC Workshop 2007,
Ulrich H. E. Hansmann, Jan Meinke, Sandipan Mohanty,
Olav Zimmermann (Editors),
John von Neumann Institute for Computing, Jülich,
NIC Series, Vol. 36, ISBN 978-3-9810843-2-0, pp. 103-107, 2007.

© 2007 by John von Neumann Institute for Computing

Permission to make digital or hard copies of portions of this work for personal or classroom use is granted provided that the copies are not made or distributed for profit or commercial advantage and that copies bear this notice and the full citation on the first page. To copy otherwise requires prior specific permission by the publisher mentioned above.

<http://www.fz-juelich.de/nic-series/volume36>

Chemical Space of Auxins, their Multi-Phenomenology and Multiple Protein Interaction

Noel Ferro^{1,2}, Patrick Bultinck³, Thomas Bredow¹, and Thomas Reinard²

¹ Institute for Physical and Theoretical Chemistry,
University of Bonn, Wegelerstr. 12, D-53115 Bonn, Germany
E-mail: Noel.ferro@genetik.uni-hannover.de

² Institute of Plant Genetic,
University of Hannover, Herrenhauser Str.2, D-30419, Germany

³ Department of Physical Chemistry,
University of Ghent, Krijgslaan 281(S3) B-9000 Gent, Belgium

The irregular net of physiological processes in plants has been the medium for intuitive theories (hypotheses) of structure-activity relationships of auxin molecules, but even now their chemical definition is unclear. Molecular Quantum Similarity Measures (MQSM) scored a conceptual framework to uncover such phenomenon. The quantum objects (auxins) were classified by cluster analysis methods based on a feed-back with a biological consensus variable. Next, standardized multi-screening bioassays of different auxins were carried out and the data analysis was implemented at multidimensional level. In these scenarios, on the one side, a new active auxin-like substance without COOH in the side chain (2, 6-dibromo-phenol) was found, and hardness (η) was shown to be a common variable to predict the auxins biological activities. On the other side, two sets of molecular properties are postulated to explain different physiological processes such as growth and morphogenesis. These dual properties of auxins are structurally consistent with the two different binding-pocket systems disclosed until now in ABP1 and TIR1, respectively.

1 Introduction

The underlying concept of the structure-activity rule, “auxins act as a kind of co-enzyme or ergon at the growth center, which is a protein or enzyme surface of highly specific shape”¹ is not consistent with experimental facts anymore.

Due to their pleiotropic effects (e.g. organogenesis, cell elongation, cell division) auxin activity depends on more than one “receptor” and on a new biochemical mechanism of interaction of protein – small molecule – protein². These statistical regularities have not been taken into account previously for the analysis of the detailed molecular causal properties of their biological activities. The physiological role of the Auxin-Binding-Protein 1 (ABP1) is still debated. But definitively, it is not involved in all the different physiological auxin effects³. Furthermore, the speculations about specialized receptor functions for specific transporters like PIN (PIN-FORMED) proteins should be considered as well^{4,5}. Recently a new complex of three proteins SCF^{TIR1} out of which the transport inhibitor response 1 (TIR1) has been described as an auxin receptor². The objective of the present article is to summarise some of our recent results and search for interactions between some methods of molecular biology and computational chemistry in order to analyse the complex physiological processes related to the auxin phenomena.

2 Structure-activity

Different approaches have been postulated: **chemical**⁶, **physico-chemical**⁷ **binding site models**^{8,9}. They can not overcome the structure-activity impasse of auxins. The unconnected comprehensions of the chemical and biological view-points have failed to describe the auxin phenomena: first, suppressing ideas of statistical regularities and evaluating the assumption, “structure generates properties”, as a dynamic regularity of the hormone-receptor interaction exported from the animal model. Second, distinctiveness of the molecular biology and biochemical outcomes in the last twenty years in plants has not been incorporated into the analysis.

3 Problem Solution

Our chemical computational-biostatistical approach focused on the auxin chemical space in the biological context. The analysis of the structure of the auxin-like molecules is treated as the invariant part, to which the biological tests are relative, but not vice versa¹⁰. That does not mean, that the phytohormone phenomenon depends exclusively on the ligand structure, but the ligand structure analysis is the point to define the degrees of freedom of the phenomenon. The analysis presented focus on:

1. searching Molecular Quantum Similarities associated with the biological activities;
2. classifying auxin molecules based on the connections of the QMSM and the Biological Activity;
3. developing standardized bioassay for the screening of selected molecules to confirm the hypothesis of relation quantum similarity – biological activity;
4. identifying quantum molecular regions responsible for the biological activity.

The statistical treatment of similarity matrices of both, Coulomb and Overlap operators, was preceded by a Principal Component Analysis, minimizing repetitive information. Next, cluster methods analysis were applied. Relationship between clusters and biological activity was confirmed by statistic methods with probability *a posteriori*. The resulting cluster allowed to recognize different quantum similarity classes related to the biological activity¹⁰. Following, the biological activity of 2,6-Br-Phe (without COOH group), active as auxin by QMSM predictions¹⁰, was experimentally confirmed¹¹.

Functionally, the multi-scaling analysis of the experimental data allowed us to discriminate two sets of chemical predictor variables (chemical regions), which distinguish two different kind of auxin biological activities: growth, where ABP1-binding activities inferred a physiological relation statistically; and morphogenesis events where TIR1 is involved (Fig. 1). Structurally, the two sets of accessory binding areas proposed M and G (Fig. 1 A) are closely related to the differences of the binding site requirements of TIR1 and ABP1 respectively (the two proposals of auxin receptors) (Fig. 1, B). In TIR1 – crystal is well represented the binding by the N-indole, while a complex binding system appear in the complex with Zn in ABP1. The results of both crystals suggest a duality of auxin properties: able to bind in two totally different systems. On the one side (ABP1), the

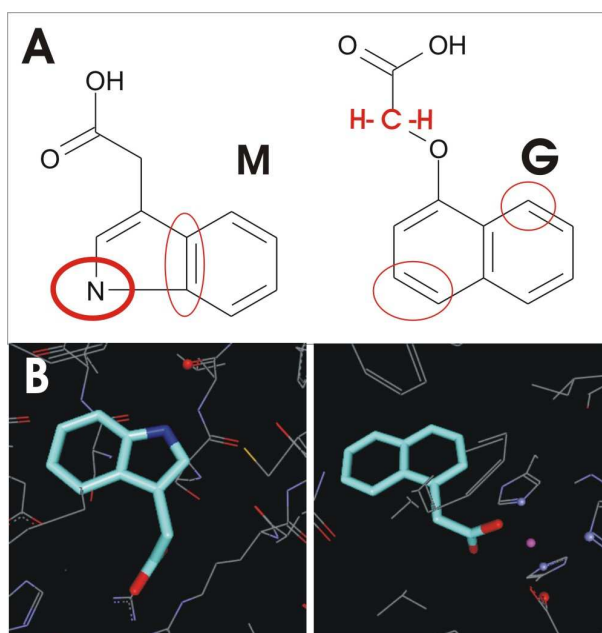


Figure 1. Accessory binding areas. (M) morphogenesis, (G) growth, (H-C-H) region buffer important for growth regulation.

molecule-protein interaction via auxin side chain evoke totally different chemical binding conditions, to which the existence of the sp^2 carbon, statistically inferred, could be important. On the other side (TIR1), the interaction via the N-indole in TIR1 was predicted before as an important point for morphogenetic events¹¹. Likewise, both crystal auxin – protein do not show any rearrangement of the atoms of the protein, due to the binding. The structural information rather suggests electron arrangement, like predicted by our calculations with a common variable influences the biological activity of auxins at every level: the chemical hardness¹¹. This is also able to classify the 240 auxins together with the two principal components obtained by QMSM (Fig. 2). Soft molecules are more active than hard molecules if electron transfer or rearrangement is necessary for the reaction¹². This concept is exactly confirmed by our results. Functional dependence with hardness having natural auxins as outliers¹¹, suggests a relation with the limits of reactivity in biological systems; it means toxicity. Contrary to the natural auxins, synthetic auxins like 2,4-D are potent herbicides and their hardness is very high. Consequently, other sites and/or inespecific interactions in the cellular systems (proteins) are expected, it dependent on the molecular structures. These results, the broad quantity of active molecules as auxins and many of them being almost as active as the standard auxin IAA, indicate controversy between a typical specificity of a hormonal mechanism and the auxin concept in plants. The strategies described above are the key of chemical design, which will result in the next generation of new synthetic auxins and/or comprehensive bases of the action mechanism. This may be also extended to the phytohormone context.

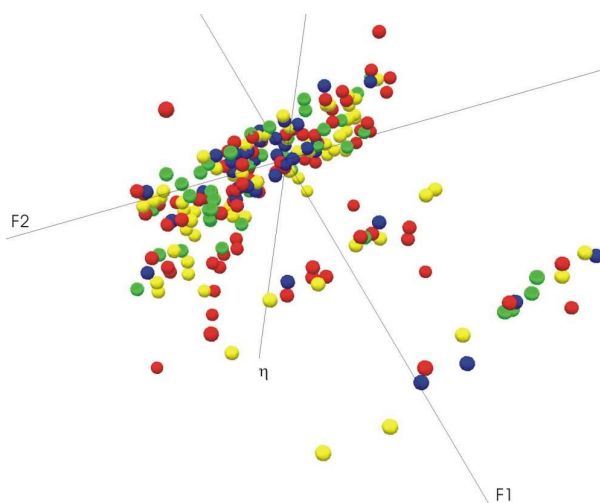


Figure 2. Influence of hardness in the classification of 241 auxin like molecules with QMSM components.

4 Conclusion

It was demonstrated that a combination of both electronic structure and intermolecular interaction descriptors was able to describe this multi-dimensional biological phenomena. The Coulomb matrix, as an electrostatic potential descriptor, was the most important differentiating auxin activity measure as evidenced by discriminant analysis. A phenol derivative, predicted as active substance, was confirmed to be active in different auxin tests. The molecular descriptors and regions analyzed functionally, from phenomenological point of view, are structurally related with the differences of both binding sites reported for ABP1 and TIR1. The electronic rearrangement in the interaction auxin - receptor predicted by hardness (η) is confirmed by non atoms rearrangements in the both auxin-ABP1 and auxin-TIR1 interactions. The existence of sp^2 carbon in the side chain turns the induction of activity of such substances at very low concentrations.

References

1. L. J. Audus, *Metabolism and mode of action*. (In: Ruhland W, ed. Encyclopediea of Plant Physiology Berlin: Springer, 1961).
2. X. Tan, L A. Calderon Villalobos, M. Sharon et al. *Mechanism of auxin perception by the TIR1 ubiquitin ligase*, Nature **446**, 640, 2007.
3. R. M. Napier, K. M. David, C. Perrot-Rechenmann, *A short history of auxin-binding proteins*, Plant Molecular Biology **49**, 339, 2002.
4. J. Friml, J. Wisniewska, E. Benkova, et al. *Lateral relocation of auxin efflux regulator PIN3 mediates tropism in Arabidopsis* Nature **415**, 806, 2002.
5. J. J. Blakeslee, A. Bandyopadhyay, W. A. Peeret, al. *Relocalization of the PIN1 auxin efflux facilitator plays a role in phototropic responses*, Plant Physiology **134**, 28, 2004.

6. C. Hansch, R. M. Muir, *The Ortho Effect in Plant Growth-Regulators*, Plant Physiology **25**, 389, 1950.
7. H. Veldstra, *The Relation of Chemical Structure to Biological Activity in Growth Substances*, Annual Review of Plant Physiology and Plant Molecular Biology **4**, 151, 1953.
8. G. F. Katekar, *Auxins - Nature of the Receptor-Site and Molecular Requirements for Auxin Activity*, Phytochemistry **18**, 223, 1979.
9. S. Tomic, R. R. Gabdoulline, B. Kojic-Prodic, R. C. Wade, *Classification of auxin plant hormones by interaction property similarity indices*, Journal of Computer-Aided Molecular Design **12**, 63, 1998.
10. N. Ferro, A. Gallegos, P. Bultinck et al. *Coulomb and Overlap Self-Similarities: A comparative selectivity analysis of structure - function relationships for auxin - like molecules*, Journal of Chemical Information and Modeling **46**, 1751, 2006.
11. N. Ferro, P. Bultinck, A. Gallegos, H.-J. Jacobsen, R. Carbo-Dorca, T. Reinard, *Unrevealed structural requirements for auxin-like molecules by theoretical and experimental evidences*, Phytochemistry **68**, 237, 2007.
12. R. G. Pearson, *Absolute Electronegativity and Hardness Correlated with Molecular-Orbital Theory*, PNAS **83**, 8440, 1986.